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(54) Title: ^{19}F LABELLED COMPOUNDS AS NMR IMAGING AND SPECTROSCOPY AGENTS

(57) Abstract

^{19}F labelled compounds are disclosed which are useful in methods of NMR imaging and spectroscopy. The compounds comprise a ^{19}F-containing sensor moiety, and a transport polymer or substrate, and can optionally also comprise a spacer moiety to separate the sensor moiety and the transport polymer.

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^{19}F LABELLED COMPOUNDS AS NMR IMAGING AND SPECTROSCOPY AGENTS

Nuclear magnetic resonance (NMR) techniques are finding increasing use in medical diagnostics. NMR imaging, or magnetic resonance imaging (MRI) as it is sometimes known, has been found to be useful in the detection of a variety of diseases and disorders. MRI has several advantages over other imaging techniques. For example, unlike computerized tomographic methods, MRI does not employ ionizing radiation, and therefore is believed to be safer. Also, MRI can provide more information about soft tissue than can some other imaging methods.

The majority of the NMR techniques developed so far have been based on imaging of hydrogen nuclei. However, other nuclei offer potential advantages with respect to NMR. ^{19}F in particular is of interest. The fluorine nucleus offers a strong NMR signal magnitude (high gyromagnetic ratio) second only to that of protons. Virtually no imagable fluorine exists naturally in the human body, so no background signal exists; any detectable signal comes only from whatever ^{19}F has been administered to the subject.

^{19}F is a stable isotope and is naturally abundant, so there is no need for isotopic enrichment. Because its gyromagnetic ratio is about 94% that of hydrogen, existing equipment designed to image protons can be inexpensively adapted for ^{19}F.

Although ^{19}F NMR has potential benefits, there is a need for new and improved ^{19}F-containing agents which can be used in NMR imaging and spectroscopy techniques.

The present invention relates to ^{19}F labelled compounds which can be used as NMR imaging and spectroscopy agents. In one aspect of the present invention, such a compound comprises a transport polymer and a ^{19}F-containing sensor moiety, and may optionally also include a spacer moiety separating the ^{19}F-containing sensor moiety and the transport polymer. Because the ^{19}F nucleus is very sensitive to changes in its steric and electronic environment, the compound can be used to sense different tissue parameters and cell properties.

The transport polymer can provide multiple substitution sites, allowing more ^{19}F-containing sensor moieties to be attached, and thereby making the signal produced by the compound easier to detect. The polymer or substrate serves the multiple purposes of anchoring the sensor moiety, targeting it, and reducing its toxicity. As to the anchoring function, the bonding can be chosen so as to keep the sensor moiety attached to the substrate, for microenvironmental monitoring, or permitting the sensor to detach and reach the interior of cells, for intracellular monitoring. The targeting function is based on the specificity of the substrate. Where that specificity is based on the stereochemical characteristics of the substrate, that specificity will not be disturbed by (a) substitution of ^{19}F for H, because the atomic radius of the two are effectively the same, (b) substitution of ^{19}F for -OH because of similar size and electronegativity.

Other substrates to which ^{19}F-containing sensor moieties can be attached include antibodies or fragments thereof, enzymes, receptor binding agents, and a variety of other biologically compatible substances.

In one embodiment of the present invention, the ^{19}F-containing sensor moiety is bonded to a spacer moiety, which is bonded to the transport polymer or substrate. The spacer moiety can be used to isolate the ^{19}F atoms from the substrate, thereby enhancing the NMR signal produced. The spacer moiety preferably contains an amino group, has a chain length of approximately 1-100 C atoms, and can optionally include one or more ^{19}F atoms. Suitable spacer moieties include alkyl, alkoxy, and alkaryl hydrocarbons which contain a primary amine group, hydrazine, hydrazide, semicarbazide, hydroxylamine, or aminophenyl.

In another embodiment of the present invention, the ^{19}F-containing sensor moiety is directly bonded to the substrate or transport polymer. For example, metabolically important substrates can be directly fluorinated and used as indicators of particular disorders.

The present invention also relates to methods of using ^{19}F-labelled compounds in methods of ^{19}F magnetic resonance imaging (MRI) or magnetic resonance spectroscopy (MRS). Such methods comprise administering to a living subject an effective amount of a ^{19}F-labelled compound as described above, and then detecting the ^{19}F NMR signal produced thereby. The compound contains an amount of ^{19}F effective to provide a detectable NMR signal.

Fluorinated compounds in accordance with the present invention have both diagnostic and prognostic uses, and can serve as physiological probes and cell-function reporters. They can be used not only to delineate tissues at risk and to characterize disease states, but also for monitoring the results of therapy. Specific uses for such compounds include vascular imaging, tumor imaging, and detection of lesions in atherosclerosis, bone metastases, and myocardial infarction. Among the physiologically important parameters that could be sensed are oxygen content, temperature, pH, and the concentration of ions such as Na+, Ca^{2+}, and Mg^{2+}.

A wide variety of transport polymers or substrates can be used in the present invention. Suitable examples include dextran polymers, aminodextrans, cyclodextrins, polylysine, polyaspargine, dextrin inclusion compounds of various sizes, highly charged molecules such as dextran sulfate, heparin, and heparin sulfate, other biocompatible polysaccharides such as hyaluronic acid or carboxymethylcellulose, polylactic acid, polyglycolic acid, and polymers synthesized by polymerizing fluorinated glucose and other sugar molecules. If, for example, the transport polymer is aminodextran, it can suitably have a molecular weight between about 100d and about 500 Kd.

When the polymer is itself fluorinated, it can be attached to a variety of other agents, such as polyclonal or monoclonal antibodies or fragments thereof, receptor binding agents, histochemicals, enzymes, hormones, antibiotics, antiviral agents, antitumor agents, proteins, or a variety of other biological substances.

Among the suitable ^{19}F-containing sensor moieties are simple fluorinated alkyls such as CH_2F, CHF_2, CF_3,

fluorinated acetates such as $COCH_2F$, $COCHF_2$, and $COCF_3$, as well as fluoroaniline (useful for sensing pH), fluorinated pyrophosphate analogs such as fluoroalkyl phosphonates, fluorinated polyamines, fluorinated porphyryns and their metal complexes, fluorinated histochemicals, and fluorinated biotin or avidin.

Methods of fluorination in accordance with the present invention can suitably be by one of the following methods.

The hydroxyl groups of a polymer can be replaced by ^{19}F atoms, using chemical, enzymatic, or a combination of chemical and enzymatic methods. Partial hydroxyl replacement can be accomplished by using diethylaminosulfur trifluoride (DAST) as a fluorinating agent.

Alternatively, CHO groups on the polymer can be replaced by ^{19}F using DAST.

As another option polymeric hydroxyl groups can be esterified, for example:

$$\text{polymer-OH} + C_2F_5COOCOC_2F_5 \rightarrow \text{polymer-OCOCF}_2CF_3$$
$$\text{polymer-OH} + ClCOC_2F_5 \rightarrow \text{polymer-OCOCF}_2CF_3$$
$$\text{polymer-OH} + CF_3COOCOCF_3 \rightarrow \text{polymer-OCOCF}_3$$
$$\text{polymer-OH} + ClCOCF_3 \rightarrow \text{polymer-O-COCF}_3$$

Also, hydroxyl groups could be oxidized using reagents such as periodate, and then coupled to the amino groups of ^{19}F-labelled compounds, then reduced with reagents such as $NaBH_4$.

Polymer hydroxyl groups could be activated by cyanogen bromide and then coupled to a fluorinated amine, yielding an iminocarbonic acid ester.

Polymer hydroxyl groups, such as in a dextran polymer, can be utilized to form 3-bromo-2-hydroxyl propyl dextrans, which can be transformed into epoxide derivatives. The epoxide derivative is highly reactive and in alkaline solution at room temperature can be coupled with substances containing nucleophilic groups like alkyl and aryl primary amines, hydroxyl groups, and thiol groups.
For example:

dextran$(OH)_3$ + 3-bromo-2-hydroxyl propyl epoxide →
3-bromo-2-hydroxy propyl dextran
Rxn with NaOH → dextran with epoxide
Rxn with RAH → dextran-$OCH_2CHOHCH_2AR$
A = O, S, NH
R = organic fluorine-containing moiety

Fluorinated amines can be attached to polysaccharides. For instance, carboxymethyl-cellulose can be esterified to produce the methyl ester which, on treatment with hydrazine hydrate, forms hydrazide. The hydrazide on diazotization with HCl and $NaNO_2$ forms a reactive azide. The azide in alkaline solution will react rapidly with amines to form the covalently bonded product polymer-CONHR, where R is a fluorinated aliphatic or aromatic amine.

CMCOOH + CH_3OH + NH_2NH_2 → $CMCOHNNH_2$
Rxn with $NaNO_2$ + HCl → $CMCON_3$
Rxn with RNH_2 → CMCONHR

Aminodextrans can be fluorinated using S-ethyl thiol trifluoroacetate (SETFA) as a fluorinating agent. Acylation of available amino groups can be accomplished by using an excess of SETFA as the acylating reagent.

Alternatively, amino groups can be acylated using acid fluorides (anhydrides).

$D\text{-}NH_2 + (CF_3CF_2CO)_2O \rightarrow D\text{-}NHCOCF_2CF_3$

$D\text{-}NH_2 + ClCO\text{-}AR \rightarrow D\text{-}NHCO\text{-}AR$

AR = aromatic ring containing F

$D\text{-}NH_2 + ClCO\text{-}AR\text{-}LF_3 \rightarrow D\text{-}NHCO\text{-}AR\text{-}LF_3$

AR = aromatic ring

L = alkyl chain

Other possible reactions include acylation using fluorinated propionic anhydride, succinic anhydride (for example - trifluoroacetamido succinic anhydride) reactions with fluorinated phenyl isothiocyanate, and reactions with fluorinated alkyl isothiocyanate.

Where antibodies or fragments thereof are used, the sensor moieties can be selectively attached to sites not directly involved in antibody-antigen binding, thereby allowing the antibody to retain its immunoreactivity. Possible sites for attachment include carbohydrate groups, amino groups, sulfhydryl groups, or combinations thereof.

The following specific examples illustrate the preparation of compounds in accordance with the present invention.

N-Trifluoroacetamide D-Glucose

Glucoseamine in anhydrous methanol was treated with s-ethyl thiol trifluoroacetate (SETFA) as described by Wolform and Conigliaro, Carbohydrate Research, 11, 63 (1969). A suspension of 2-amino-deoxy-D-glucose hydrochloride (10 g) in 50 ml anhydrous methanol was treated with an equivalent amount of sodium methoxide in methanol (1.06 g of Na in 10 ml methanol). The mixture was stirred (magnetic stirrer) till a clear solution was obtained. NaCl precipitate remained at the bottom. To this, SETFA (10 g) was added. The reaction mixture was stirred at room temperature for 24 hrs. The solution was evaporated to a solid residue and the residue was extracted with hot acetone. Ether was added to the cooled acetone extract and the mixture was refrigerated overnight. The white crystalline compound was recrystallized from a mixture of acetone-ether to obtain shiny crystals.

Results

Yield: 8.2 g. MP: 193-195°C.

Analysis

Element:	C	H	N	F
Calculated:	34.92	4.40	5.09	20.72
Found:	36.89	4.75	4.92	20.75

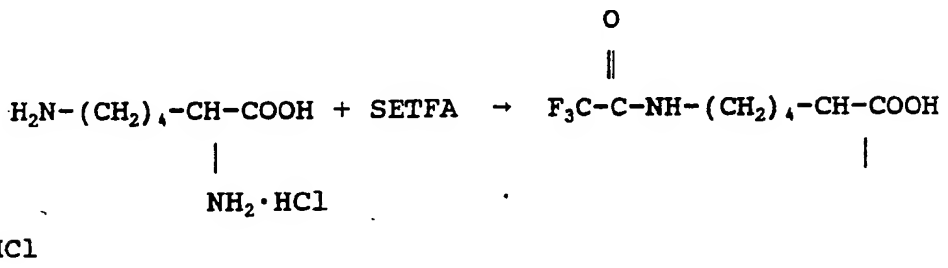
The product was soluble in water. Elemental analysis data were in agreement with the calculated values.

Proton and F-19 NMR data confirmed the formation of N-trifluoroacetamido-D-glucose.

2-deoxy-glucose NH_2HCl + SETFA $\xrightarrow{\text{MeONa in MeOH}}$ 2-deoxyglucose-NH-$COCF_3$.

Trifluoroacetyl-DL-Lysine

Trifluoroacetyl-DL-lysine was obtained by treating DL-lysine monohydrochloride with s-ethyl thiol trifluoro acetate (SETFA) in basic solution, as described in Schallenberg and Calvin, JACS 77, 2779 (1955).



$NH_2 \cdot HCl$

SETFA (4.0 ml) was added to DL-lysine monohydrochloride 3.6 g (20 mmol), dissolved in 20 ml of 1N NaOH. The heterogeneous mixture was stirred for 6 hours at room temperature and cooled for 1 hour in an ice cold water bath. The solid that separated was filtered and washed with cold water. It was recrystallized from ethanol.

Results

Yield: 0.8 g (16%) (Loss of product due to washing with cold water).

MP: 262-263°C

H-1 NMR: 3.82 δ CH; J = 1.5, 1.7, 1.96, 3.41 (Solvent D_2O).

F-19 NMR: Sharp signal (solvent D_2O).

Elemental Analysis:	C	H	N	F
Found:	39.87	5.45	11.61	23.52
Calculated:	39.67	5.41	11.57	23.55

Aminodextrans

Aminodextrans (molecular weight: 10k, 40k, and 70k) were obtained from Molecular Probes, Inc., Portland, Oregon.

Molecular Size	Number of amino groups per molecule
10k	6.8
40k	13
70k	30

Aminodextran molecule was reacted with s-ethyl thioltrifluoracetate (SETFA) in a formamide and pyridine mixture to yield a product in which the amino groups of the aminodextrans were modified with trifluoracetyl moiety, as described in Goldberg and Anfinsen, Biochem., 1, 401 (1962).

$$\text{Dextran-NH}_2 + \text{CF}_3\text{COSC}_2\text{H}_5 \rightarrow \text{Dextran-NHCOCF}_3 + \text{C}_2\text{H}_5\text{SH} \uparrow$$

The general synthesis procedure was as follows: Aminodextran was dissolved in formamide and pyridine (2:1 v/v). S-ethylthioltrifluoroacetate (SETFA) was added slowly with stirring. The mixture was stirred overnight. The desired product was precipitated with cold ethanol and further purified by dialysis against water, and the powdered product obtained by lyophilization.

As a specific example, aminodextran 70k (0.6 g) was dissolved in 10 ml formamide by stirring for 2-3 hours. Pyridine 5 ml was added, and stirring continued until the homogeneous solution was obtained. The pH was approximately 7 by paper. S-ethylthioltrifluoroacetate 3 ml was added dropwise for a period of 30 minutes with vigorous stirring. This reagent is immiscible with the above solvent system. However, it forms small droplets and slowly undergoes reaction which could be seen by the fall in pH values and homogeneity of the solution. The

mixture was stirred overnight and poured on chilled (-12°C) absolute ethanol (150 ml) with vigorous stirring. The white precipitate obtained was held at -12°C for an additional 4 hours with stirring. The precipitated product was centrifuged and washed with ethyl alcohol. The product was dissolved in distilled water and dialyzed against distilled water for 24 hours with 6 changes using 1000 ml of water each time. The dialyzed solution was centrifuged and the clear solution was lyophilized to obtain a white silky solid.

Yield: 0.56 g
TLC Matrix: silica gel 60A, MK6F, Whatman
Solvent: Pyridine/acetic/acid water (9:1:90, v/v/v)
Detection: 50% H_2SO_4
R_f of starting material: 0.41
R_f of final product: 0.74
Proton NMR spectra: Typical polymeric appearance
F-19 NMR spectra: Single (Fluorine) sharp signal

Elemental Analysis

	C	H	N	F
Calculated*:	43.87	5.94	1.11	2.88
Found:	40.65	5.78	0.62	2.26

*percentages of elements calculated by assuming the molecular weight of dextran to be 70k.

Results

Trifluoroacetylated aminodextran 10K and 40K:

10K: TLC analysis:
Solvent system: pyridine/acetic acid/H_2O (9:1:90)
R_f of starting material: 0.5
R_f of final product: 0.84

NMR spectra analysis:

Proton spectra: Typical polymeric compounds (D_2O)

F-19 spectra: Single fluorine, sharp signal (D_2O)

Elemental analysis:

	C	H	N	F
Found:	40.01	5.65	0.83	2.50
Calculated*:	43.56	5.81	1.39	4.13

*percentages of elements calculated by assuming the molecular weight of dextran to be 10K.

40K: TLC analysis:

Solvent system: pyridine/acetic acid/H_2O (9:1:90)

R_f of starting material: 0.48

R_f of final product: 0.76

NMR spectra analysis:

Proton spectra: Typical polymeric (D_2O)

F-19 spectra: Single fluorine, sharp signal (D_2O)

Elemental analysis:

	C	H	N	F
Found:	40.82	5.97	0.61	1.58
Calculated*:	43.92	5.98	0.99	2.35

*percentages of elements by assuming the molecular weight of dextran to be 40K.

Trifluoacetylation of Poly-L-Lysine

General Procedure:

Trifluoroacetylation of poly-L-lysine is carried out with S-ethyl thioltrifluoroacetate in dimethylformamide, as described in Levy and Paselk, Biochem. Biophys. Acta, 310, 398-405 (1973). The amino groups of poly-L-lysine are modified with the trifluoroacetyl moiety.

Poly-L-lysine·HBr (molecular weight 8,800) was reacted with S-ethyl-thioltrifluoroacetate in dimethylformamide. Poly-L-lysine·HBr (100 mg, 11.36 μmoles) was dissolved in 20 ml of DMF with stirring, for 30 minutes when an almost clear solution was obtained. Triethylamine (TEA) 50 μl was added (appearance of precipitate noted) and the stirring continued for 15 minutes. S-ethylthioltrifluoroacetate (SETFA 51.737 mg, 327.17 μmoles), dissolved in 1 ml of DMF, was added dropwise to the reaction mixture with constant stirring for 15 minutes. The pH was adjusted after each addition of SETFA. A clear solution obtained at the end, was stirred for another 90 minutes and then poured onto chilled absolute ether. The solution was decanted. The precipitate was centrifuged and then dissolved in 15-20 ml water and dialyzed against distilled water at 4·C for 48 hours. The shiny powdery product was obtained by lyophilization of the dialyzed solution.

Results

Yield: 20 mgs

F-19 NMR spectra: A sharp single fluorine signal (D_2O)

Trifluoroacetamido-succinylated Poly-L-Lysine: Poly-L-Lysine (50 mg, 5.68 μ Mol) in 20 ml phosphate buffer (pH=7.24) was reacted with (120 mg) trifluoroacetamido-succinic anhydride for 30 minutes. General procedure for preparation of succinylated Poly-L-Lysine is described by W. B. Stason, M. Vallotton and E.

Haber; Biochem. Biophys. Acta. 133:582-584 (1967). The product was purified by exhaustive dialysis against d. water and lyophilized to obtain white solid.

* * *

One way of producing a stronger signal from trifluoroacetylated aminodextrans would be to trifluoroacetylate the hydroxyl groups instead of the amino groups, which will dramatically increase the number of available sites, and therefore increase the concentration of ^{19}F in the molecule. The in vivo NMR signal can also be optimized by using spacer moieties to separate the ^{19}F from the substrate.

In the NMR methods of the present invention, the ^{19}F-labelled compound is administered to a living subject, preferably parenterally or orally. They can suitably be administered in a formulation containing one or more of the ^{19}F-labelled compounds and a pharmaceutically acceptable diluent or carrier.

* * *

The preceding description is intended to illustrate specific embodiments of the present invention, not to provide an exhaustive description of all possible embodiments of the invention. Persons skilled in this field will recognize that modifications could be made to the preceding examples which would still be within the scope of the present invention.

CLAIMS:

1. A ^{19}F labelled NMR compound, comprising:
a ^{19}F-containing sensor moiety; and
a transport polymer;
where the amount of ^{19}F contained by the compound is effective to provide a detectable NMR signal.

2. The compound of claim 1, where the transport polymer is selected from the group consisting of dextran polymers, aminodextrans, cyclodextrins, polylysine, polyaspargine, heparin, hyaluronic acid, carboxymethylcellulose, polylactic acid, and polyglycolic acid.

3. The compound of claim 1, where the ^{19}F-containing moiety is selected from the group consisting of fluorinated alkyls, fluorinated acetates, fluoroaniline, and fluoroalkyl phosphonates.

4. The compound of claim 1, where the ^{19}F-containing moiety is trifluoroacetate and the transport polymer is aminodextran having a molecular weight between approximately 100 kd and 500 kd.

5. The compound of claim 1, further comprising a spacer moiety, with the ^{19}F-containing sensor moiety and transport polymer being separately attached to the spacer moiety.

6. The compound of claim 5, where the spacer moiety is an alkyl hydrocarbon having a chain length of approximately 1-100 C atoms and containing an amino group.

7. The compound of claim 5, where the spacer moiety is selected from the group consisting of alkyl, alkoxy, aryl, and alkaryl hydrocarbons which contain an amino group, hydrazine, hydrazide, semicarbazide, and hydroxylamine.

8. N-trifluoroacetamido D-glucose.

9. Trifluoroacetyl-DL-lysine.

10. Trifluoroacetyl-poly-L-lysine.

11. Trifluoroacetamido succinylated poly-L-lysine.

12. Trifluoroacetylated aminodextran, where the aminodextran has a molecular weight between approximately 100 d and 500 kd.

13. A ^{19}F-labelled NMR agent, comprising:
a ^{19}F-containing sensor moiety; and
a substrate selected from the group consisting of antibodies, antibody fragments, receptor binding agents, histochemicals, enzymes, hormones, antibiotics, antiviral agents, antitumor agents, and proteins.

14. The agent of claim 13, where the ^{19}F-containing sensor moiety is selected from the group consisting of fluorinated alkyls, fluorinated acetates, fluoroaniline, and fluoroalkyl phosphonates.

15. A method of NMR imaging or spectroscopy, comprising the steps of administering to a living subject a ^{19}F labelled NMR agent in accordance with claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 in an amount effective to provide a detectable NMR signal; and then detecting the ^{19}F NMR signal produced thereby.

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INTERNATIONAL SEARCH REPORT

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I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 49/00 C 07 C 233/47 C 07 H 13/04
C 07 K 7/10 C 08 B 37/02 C 08 G 69/10

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 K C 08 B

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	Database WPI(L), Derwent no. 88-195824, & JP, A, 63135337 (ASAHI KASEI KOGYO) 7 June 1988, see the whole abstract	1,3,13, 14
Y	EP,A,0186947 (NYEGAARD & CO. A/S) 9 July 1986, see page 2, paragraph 4 - page 5, paragraph 2; page 6, paragraph 3; page 10, paragraph 3	1-7
Y	US,A,4612185 (DEAN) 16 September 1986, see column 2, line 22 - column 3, line 55	1-7
Y	US,A,4639364 (HOEY) 27 January 1987, see column 2, line 22 - column 3, line 33	1-7

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25-11-1991	21. 01. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Miss T. MORTENSEN

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 75, no. 11, 1971, abstract 77211a, & J. Chem. Soc. D (10), 512-13, see abstract	8
Y		11
X	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 78, no. 7, 1972, abstract 39873x, & Carbohyd. Res. , 24(1)218-19, see abstract	8
X	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 77, no. 15, 1972, abstract 102186x, & J. Chromatogr., 68(1), 262-3, see abstract	9
X	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 81, no. 15, 1974, abstract 91911j, & Synthesis, (6), 420-422, see abstract	9
X	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 107, no. 5, 1987, abstract 40320p, & Polymer, 28(1), 147-154, see abstract	10
Y		11
Y	File Server STN, Karlsruhe, File Chemical Abstracts, vol. 78, no. 1, 1972, abstract 4443e, & Khim. Prir. Soedin. (3), 266-71, see abstract	12
Y	File Server Derwent, Database WPI, accession no. 73-33347u [23], & JP, B, 48017750 (MEITO SANGYO Co. LTD) see abstract	12

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 15 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): methods for treatment of the human and animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claim numbers 1-7,13,14 searched incompletely because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

The term "sensor moiety" used in the claims is vague, the meaning and scope of this term has been interpreted from its definition given in the description,examples and claims. Similarly the term "transport polymer" used in the claims is vague,and has been interpreted in the same way. See PCT Article 6.

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [X] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. Claims 1-7,13,14,19
2. Claims 8,9
3. Claims 10-12

1. [X] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[X] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9101150 SA 45522

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 07/01/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0186947	09-07-86	SE-B- 465907	18-11-91
		JP-A- 61155337	15-07-86
		SE-A- 8405499	02-05-86
		US-A- 4986980	22-01-91
US-A- 4612185	16-09-86	None	
US-A- 4639364	27-01-87	US-A- 4913853	03-04-90